CHAPTER 1. INTRODUCTION, OVERVIEW, AND CONCLUSIONS

CONTENTS

Introduction

Organization and Development of the 1984 Report

Each year the Office on Smoking and Health (OSH), working in close collaboration with scientists, researchers, and others, compiles the annual Surgeon General's Report *The Health Consequences of Smoking* for submission to the U.S. Congress as part of the Department's responsibility to report new and current information on the topic as required under Public Law 91-222. This Report is the third to examine in detail specific disease entities related to smoking. The 1982 Report was a comprehensive assessment of the relationship between tobacco use and various cancers, and the 1983 Report examined this relationship for cardiovascular diseases. The 1984 volume represents a state-of-the-art comprehensive review of tobacco use and the development of chronic obstructive lung diseases.

The scientific content of this Report is the work of experts in the field of chronic obstructive lung disease research both within the Department of Health and Human Services and from outside the Federal Government. Individual manuscripts were written by experts who are nationally and internationally recognized for their scientific understanding of the etiology of chronic obstructive lung diseases, particularly the relationship with cigarette use.

Manuscripts received from authors were extensively reviewed by numerous outside experts familiar with these specific areas. The entire Report was then submitted to a broad-based panel of 11 distinguished lung disease experts and to experts within the U.S. Public Health Service for their review and comments.

The 1984 Report includes a Foreword by the Assistant Secretary for Health of the Department of Health and Human Services and a Preface by the Surgeon General of the U.S. Public Health Service. The body of the Report consists of 10 chapters, as follows:

- Chapter 1. Introduction, Overview, and Conclusions
- Chapter 2. Effect of Cigarette Smoke Exposure on Measures of Chronic Obstructive Lung Disease Morbidity
- Chapter 3. Mortality From Chronic Obstructive Lung Disease Due to Cigarette Smoking
- Chapter 4. Pathology of Lung Disease Related to Smoking
- Chapter 5. Mechanisms by Which Cigarette Smoke Alters the Structure and Function of the Lung
- Chapter 6. Low Yield Cigarettes and Their Role in Chronic Obstructive Lung Disease
- Chapter 7. Passive Smoking
- Chapter 8. Deposition and Toxicity of Tobacco Smoke in the Lung

Historical Perspective

The relationship between cigarette smoking and chronic obstructive lung disease (COLD) was among the first recognized and is now the best understood of the diseases caused by smoking. Sigmund reported as early as 1870 that heavy smokers suffered "affections" of the nose, mouth, and throat more frequently and in a more virulent fashion. In 1897, Mendelssohn reported the incidence of "affections" of the respiratory tract to be 60 percent greater in smokers than in nonsmokers, as well as somewhat greater in those who inhaled compared with smokers who did not inhale.

Overview

Scientists from a variety of disciplines have investigated the role of cigarette smoking in the development of COLD; today we can trace the progressive decline in lung function in smokers with increasing smoke exposure, describe the concurrent pathologic changes, demonstrate that both COLD prevalence and COLD death are limited largely to smokers, and describe in detail a plausible mechanism by which cigarette smoking can lead to the development of emphysema. Some gaps in the understanding of the details of this process may still exist, but the experimental and epidemiologic evidence leaves no room for reasonable doubt on the fundamental issue: cigarette smoking is the major cause of COLD in the United States.

The earliest recognized response to cigarette smoke is an increase in airway resistance that occurs with the inhalation of smoke by the smoker. This increase in resistance is a response to the irritants in the smoke, as is coughing, which is more frequent in smokers than in nonsmokers, even among adolescents. By the time smokers become young adults, a substantial proportion of them will have developed pathologic changes in their small airways. These abnormalities are demonstrable using a variety of physiologic tests, and are a result of pathologic changes or inflammation in the airways less than 2 mm in diameter. Part of this small airways response, but perhaps a later manifestation of it, is the development of smooth muscle hypertrophy, goblet cell hyperplasia, and mild peribronchiolar fibrosis. The prevalence of abnormalities on tests of small airways function increases as these young smokers grow older, and is greater in heavy smokers than in light smokers. While it is clear that changes in the small airways represent an early response to cigarette smoking and that they are a significant finding in the pathophysiology of COLD, it is not clear that abnormal function of the small airways, per se, is

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useful as a marker for identifying who will progress to develop symptomatic COLD. It may identify a large group of smokers who manifest an irritant response to smoke in the small airways, of whom only a subset actually develop symptomatic airflow obstruction.

Measurable differences in tests of expiratory airflow exist between smokers and nonsmokers after age 25. Smokers as a group have a more rapid decline in FEV_1 with age than that observed in nonsmokers, and the decline is even greater among heavy smokers. However, this increased rate of decline in lung function is not distributed evenly, even among smokers with similar smoking histories. Some smokers have a far more rapid decline than the average smoker, and clearly those individuals who have developed symptomatic chronic airflow obstruction have had a larger total decline in lung function than the average smoker. This has led to the suggestion that individuals with a particularly rapid decline in FEV_1 early in life may represent a group especially susceptible to the later development of symptomatic COLD. The nature of this susceptibility remains unclear, but differences in depth or pattern of inhalation, variations in the cellular and biochemical response of the lung to smoke, differences in immune or repair mechanisms, and childhood infections or exposure to environmental tobacco smoke as a child have been suggested as potential factors.

The accumulation of lung damage, marked by the excess decline in FEV_1 and other measures of expiratory airflow, can lead to shortness of breath and other symptoms that characterize clinically significant COLD. These symptoms can result in disability due to ventilatory limitation and may vary from patient to patient in severity and duration. Many patients with clinically disabling COLD die with the disease rather than because of it. Death from COLD usually results only after extensive lung damage and commonly occurs because of failure of the severely damaged lungs to maintain adequate gas exchange.

The cessation of cigarette smoking has a substantial salutary impact on the incidence and progression of COLD. Cigarette smokers who quit prior to developing abnormal lung function are unlikely to go on to develop ventilatory limitation; when the abnormalities are demonstrable only on tests of small airways function, cessation often results in a reversal of these changes and a return to normal function. The presence of significant fixed reduction in measures of expiratory airflow usually reflects the presence of substantial lung damage. Cessation of smoking at this stage of COLD results in a slowing in the rate of decline in lung function with age, in comparison with that in continuing smokers. After a period of cessation, this rate of decline in function may approximate the rate found in nonsmokers, but there is little evidence to suggest that

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those who quit are able to regain their prior excess functional loss. Therefore, those who quit continue to have reduced lung function when compared with those who have never smoked, but their lung function begins to decline less rapidly with age when compared to the lung function of those who continue to smoke.

The importance of cigarette smoking as a causative factor in COLD is emphasized by cross-sectional studies of populations in the United States where often the only major predictor for developing or dying of COLD is smoking behavior. In the absence of cigarette smoking, clinically significant COLD is rare.

As the smoker enters the sixth decade of life, pathologically definable pulmonary emphysema begins to become evident. In older age groups, mild to moderate emphysema is present in most smokers and is rare in nonsmokers. Once again, however, only a small percentage of smokers develop severe emphysema; this minority includes a disproportionate number of heavy smokers.

A mechanism for smoking-induced emphysematous lung injury has been proposed and continues to evolve as our understanding of cellular and biochemical responses of the lung increases. Emphysema can be produced by the presence of excessive amounts of elastase (an enzyme capable of degrading the structural elements of lung tissue) or by the absence of α_1-antiprotease (a protein that inhibits the action of elastase). As part of the inflammatory response to cigarette smoke, an increased number of inflammatory cells are present in the lungs of smokers; these cells may result in an increased amount of elastase being present in the lung. In addition, cigarette smoke can oxidize the α_1-antiprotease in the lung, further contributing to the imbalance between levels of elastase and levels of α_1-antiprotease. The net result can be excess elastase activity, leading to degradation of elastin in the lung, destruction of alveolar walls, and development of emphysema.

The text of this Report discusses in detail the relationship of cigarette smoking to COLD morbidity and mortality, the pathology of smoking-induced COLD, some of the mechanisms by which smoking results in COLD, the impact on the lung of low tar and nicotine cigarettes and of involuntary smoke exposure, the deposition and toxicology of tobacco smoke, and the role of the physician and of community intervention programs in smoking cessation.

The overall conclusion of this Report is clear: **Cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women. The contribution of cigarette smoking to chronic obstructive lung disease morbidity and mortality far outweighs all other factors.**

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Conclusions of the 1984 Report

COLD Morbidity

1. Cigarette smoking is the major cause of COLD morbidity in the United States; 80 to 90 percent of COLD in the United States is attributable to cigarette smoking.
2. In population-based studies in the United States, cigarette smoking behavior is often the only significant predictor for the development of COLD. Other factors improve the predictive equation only slightly, even in those populations where they have been found to exert a statistically significant effect.
3. In spite of over 30 years of intensive investigation, only cigarette smoking and α_1-antiprotease deficiency (a rare genetic defect) are established causes of clinically significant COLD in the absence of other agents.
4. Within a few years after beginning to smoke, smokers experience a higher prevalence of abnormal function in the small airways than nonsmokers. The prevalence of abnormal small airways function increases with age and the duration of the smoking habit, and is greater in heavy smokers than in light smokers. These abnormalities in function reflect inflammatory changes in the small airways and often reverse with the cessation of smoking.
5. Both male and female smokers develop abnormalities in the small airways, but the data are not sufficient to define possible sex-related differences in this response. It seems likely, however, that the contribution of sex differences is small when age and smoking exposure are taken into account.
6. There is, as yet, inadequate information to allow a firm conclusion to be drawn about the predictive value of the tests of small airways function in identifying the susceptible smoker who will progress to clinical airflow obstruction.
7. Smokers of both sexes have a higher prevalence of cough and phlegm production than nonsmokers. This prevalence increases with an increasing number of cigarettes smoked per day and decreases with the cessation of smoking.
8. Differences between smokers and nonsmokers in measures of expiratory airflow are demonstrable by young adulthood and increase with number of cigarettes smoked per day.
9. The rate of decline in measures of expiratory airflow with increasing age is steeper for smokers than for nonsmokers; it is also steeper for heavy smokers than for light smokers. After the cessation of smoking, the rate of decline of lung function with increasing age appears to slow to approximately that seen in nonsmokers of the same age. Only a minority of smokers will develop clinically significant COLD, and this group will have

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demonstrated a more extensive decline in lung function than the average smoker. The data are not yet available to determine whether a rapid decline in lung function early in life defines the subgroup of smokers who are susceptible to developing COLD.

10. Clinically significant degrees of emphysema occur almost exclusively in cigarette smokers or individuals with genetic homozygous α_1-antiprotease deficiency. The severity of emphysema among smokers increases with the number of cigarettes smoked per day and the duration of the smoking habit.

COLD Mortality

1. Data from both prospective and retrospective studies consistently demonstrate a uniform increase in mortality from COLD for cigarette smokers compared with nonsmokers. Cigarette smoking is the major cause of COLD mortality for both men and women in the United States.

2. The death rate from COLD is greater for men than for women, most likely reflecting the differences in lifetime smoking patterns, such as a smaller percentage of women smoking in past decades, and their smoking fewer cigarettes, inhaling less deeply, and beginning to smoke later in life.

3. Differences in lifetime smoking behavior are less marked for younger age cohorts of smokers. The ratio of male to female mortality from COLD is decreasing because of a more rapid rise in mortality from COLD among women.

4. The dose of tobacco exposure as measured by number of cigarettes or duration of habit strongly affects the risk for death from COLD in both men and women. Similarly, people who inhale deeply experience an even higher risk for mortality from COLD than those who do not inhale.

5. Cessation of smoking leads eventually to a decreased risk of mortality from COLD compared with that of continuing smokers. The residual excess risk of death for the ex-smoker is directly proportional to the overall lifetime exposure to cigarette smoke and to the total number of years since one quit smoking. However, the risk of COLD mortality among former smokers does not decline to equal that of the never smoker even after 20 years of cessation.

6. Several prospective epidemiologic studies examined the relationship between pipe and cigar smoking and mortality from COLD. Pipe smokers and cigar smokers also experience higher mortality from COLD compared with nonsmokers; however, the risk is less than that for cigarette smokers.

7. There are substantial worldwide differences in mortality from COLD. Some of these differences are due to variations in

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terminology and in death certification in various countries. Emigrant studies suggest that ethnic background is not the major determinant for mortality risk due to COLD.

Pathology of Cigarette-Induced Disease

1. Smoking induces changes in multiple areas of the lung, and the effects in the different areas may be independent of each other. In the bronchi (the large airways), smoking results in a modest increase in size of the tracheobronchial glands, associated with an increase in secretion of mucus, and in an increased number of goblet cells.
2. In the small airways (conducting airways 2 or 3 mm or less in diameter consisting of the smallest bronchi and bronchioles) a number of lesions are apparent. The initial response to smoking is probably inflammation, with associated ulceration and squamous metaplasia. Fibrosis, increased muscle mass, narrowing of the airways, and an increase in the number of goblet cells follow.
3. Inflammation appears to be the major determinant of small airways dysfunction and may be reversible after cessation of smoking.
4. The most obvious difference between smokers and nonsmokers is respiratory bronchiolitis. This lesion may be an important cause of abnormalities in tests of small airways function, and may be involved in the pathogenesis of centrilobular emphysema. The severity of emphysema is clearly associated with smoking, and severe emphysema is confined largely to smokers.

Mechanisms of COLD

1. Increased numbers of inflammatory cells are found in the lungs of cigarette smokers. These cells include macrophages and, probably, neutrophils, both of which can release elastase in the lung.
2. Human neutrophil elastase produces emphysema when instilled into animal lungs.
3. Alpha$_1$-antiprotease inhibits the action of elastase, and a very small number of people with a homozygous deficiency of α_1-antiprotease are at increased risk of developing emphysema. The α_1-antiprotease activity has been shown to be reduced in the bronchoalveolar fluids obtained from cigarette smokers and from rats exposed to cigarette smoke.
4. The protease–antiprotease hypothesis suggests that emphysema results when there is excess elastase activity as the result of increased concentrations of inflammatory cells in the lung

and of decreased levels of α_1-antiprotease secondary to oxidation by cigarette smoke.

5. Cigarette smokers have been shown to have a more rapid fall in antibody levels following immunization for influenza than nonsmokers. Whole cigarette smoke has been shown to depress the number of antibody-forming cells in the spleens of experimental animals.

6. Cigarette smoke produces structural and functional abnormalities in the airway mucociliary system.

7. Short-term exposure to cigarette smoke causes ciliostasis in vitro, but has inconsistent effects on mucociliary function in man. Long-term exposure to cigarette smoke consistently causes an impairment of mucociliary clearance. This impairment is associated with epithelial lesions, mucus hypersecretion, and ciliary dysfunction.

8. Chronic bronchitis in smokers and ex-smokers is characterized by an impairment of mucociliary clearance.

9. Both the particulate phase and the gas phase of cigarette smoke are ciliotoxic.

Low Tar and Nicotine Cigarettes

1. The recommendation for those who cannot quit to switch to smoking cigarette brands with low tar and nicotine yields, as determined by a smoking-machine, is based on the assumption that this switch will result in a reduction in the exposure of the lung to these toxic substances. The design of the cigarette has markedly changed in recent years, and this may have resulted in machine-measured tar and nicotine yields that do not reflect the real dose to the smoker.

2. Smoking-machines that take into account compensatory changes in smoking behavior are needed. The assays could provide both an average and a range of tar and nicotine yields produced by different individual patterns of smoking.

3. Although a reduction in cigarette tar content appears to reduce the risk of cough and mucus hypersecretion, the risk of shortness of breath and airflow obstruction may not be reduced. Evidence is unavailable on the relative risks of developing COLD consequent to smoking cigarettes with the very low tar and nicotine yields of current and recently marketed brands.

4. Smokers who switch from higher to lower yield cigarettes show compensatory changes in smoking behavior: the number of puffs per cigarette is variably increased and puff volume is almost universally increased, although the number of cigarettes smoked per day and inhalation volume are generally

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unchanged. Full compensation of dose for cigarettes with lower yields is generally not achieved.

5. Nicotine has long been regarded as the primary reinforcer of cigarette smoking, but tar content may also be important in determining smoking behavior.

6. Depth and duration of inhalation are among the most important factors in determining the relative concentration of smoke constituents that reach the lung. Considerable interindividual variation exists between smokers with respect to the volume and duration of inhalation. This variation is likely to be an important factor in determining the varying susceptibility of smokers to the development of lung disease.

7. Production of low tar and nicotine cigarettes has progressed beyond simple reduction in tobacco content. Additives such as artificial tobacco substitutes and flavoring extracts have been used. The identity, chemical composition, and adverse biological potential of these additives are unknown at present.

Passive Smoking

1. Cigarette smoke can make a significant, measurable contribution to the level of indoor air pollution at levels of smoking and ventilation that are common in the indoor environment.

2. Nonsmokers who report exposure to environmental tobacco smoke have higher levels of urinary cotinine, a metabolite of nicotine, than those who do not report such exposure.

3. Cigarette smoke in the air can produce an increase in both subjective and objective measures of eye irritation. Further, some studies suggest that high levels of involuntary smoke exposure might produce small changes in pulmonary function in normal subjects.

4. The children of smoking parents have an increased prevalence of reported respiratory symptoms, and have an increased frequency of bronchitis and pneumonia early in life.

5. The children of smoking parents appear to have measurable but small differences in tests of pulmonary function when compared with children of nonsmoking parents. The significance of this finding to the future development of lung disease is unknown.

6. Two studies have reported differences in measures of lung function in older populations between subjects chronically exposed to involuntary smoking and those who were not. This difference was not found in a younger and possibly less exposed population.

7. The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and pulmonary function changes in patients with asthma.

Deposition and Toxicity of Tobacco Smoke in the Lung

1. The mass median aerodynamic diameter of the particles in cigarette smoke has been measured to average approximately 0.46 μm, and particulate concentrations have been shown to range from 0.3×10^9 to 3.3×10^9 per milliliter.
2. The particulate concentration of the smoke increases as the cigarette is more completely smoked.
3. Particles in the size range of cigarette smoke will deposit both in the airways and in alveoli; models predict that 30 to 40 percent of the particles within the size range present in cigarette smoke will deposit in alveolar regions and 5 to 10 percent will deposit in the tracheobronchial region.
4. Acute exposure to cigarette smoke results in an increase in airway resistance in both animals and humans.
5. Exposure to cigarette smoke results in an increase in pulmonary epithelial permeability in both humans and animals.
6. Cigarette smoke has been shown to impair elastin synthesis in vitro and elastin repair in vivo in experimental animals (elastin is a vital structural element of pulmonary tissue).

Role of the Physician in Smoking Cessation

1. At least 70 percent of North Americans see a physician once a year. Thus, an estimated 38 million of the 54 million adults in the United States who smoke cigarettes could be reached annually with a smoking cessation message by their physician.
2. Current smoking prevalence among physicians in the United States is estimated at 10 percent.
3. While the majority of persons who smoke feel that physician advice to quit or cut down would be influential, there is a disparity between physicians' and patients' estimates of cessation counseling, with physician advice being reported by only approximately 25 percent of current smokers.
4. Studies of routine (minimal) advice to quit smoking delivered by general practitioners have shown sustained quit rates of approximately 5 percent. Followup discussions enhance the effects of physician advice.
5. A median of 20 percent of pregnant women who smoke quit spontaneously during pregnancy. That proportion can be doubled by an intervention consisting of health education, behavioral strategies, and multiple contacts.
6. Large controlled trials of cardiovascular risk reduction have demonstrated that counseling on individual specific risk factors, including smoking cessation techniques, can be effective.
7. Studies of pulmonary and cardiac patients indicate that severity of illness is positively related to increased compliance

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in smoking cessation. Survivors of a myocardial infarction have smoking cessation rates averaging 50 percent.

8. Nicotine chewing gum has been developed as a pharmacological aid to smoking cessation, primarily to alleviate withdrawal symptoms. Cessation studies conducted in offices of physicians who prescribe the gum have produced mixed results, however, with outcome depending on motivation and intensity of adjunctive support or followup.

9. Physician-assisted intervention quit rates vary according to the type of intervention, provider performance, and patient group. In general, quit rates in recent research appear to be lower than in older studies.

Community Studies of Smoking Cessation and Prevention

1. Community studies of smoking cessation and prevention are becoming an established paradigm for public health action research. Such studies emphasize large-scale delivery systems, such as the mass media, and include community organization programs seeking to stimulate interpersonal communication in ways that are feasible on a large-scale basis.

2. Although there are methodological limitations to nearly all communitywide studies, the results yield fairly consistent positive results, indicating that large-scale programs to reduce smoking can be effective in whole populations. Person-to-person communication appears to be a necessary part of a successful community program to reduce smoking.

3. Further research is needed, with both improved methodology and more emphasis on low socioeconomic status groups that have not yet shown population trends toward reduced smoking.

4. Several promising directions for research are clear, but the most important future trends will be toward the establishment of smoking reduction programs within existing health services, the combination of chronic disease prevention with mental health promotion via mass media and community intervention, and the development of social policy to establish integrated strategies for smoking cessation and prevention.

CHAPTER 2. EFFECT OF CIGARETTE SMOKE EXPOSURE ON MEASURES OF CHRONIC OBSTRUCTIVE LUNG DISEASE MORBIDITY

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INTRODUCTION

This chapter describes the sequential development of smoking-induced chronic lung disease, traced from the early structural changes limited to the small airways to the severe and widespread changes involving the small airways, large airways, and lung parenchyma. Chronic obstructive lung disease (COLD) develops relatively slowly, and the progression of lung injury and alterations in function can be followed using an individual smoker's symptoms and performance on a variety of pulmonary function tests. Early in the duration of the smoking behavior, a person may be asymptomatic, but often there are abnormalities demonstrable in the small airways that probably represent an inflammatory response to the constituents of cigarette smoke. Later, usually after 20 or more years of smoking, a constellation of symptoms and functional changes may develop, particularly in heavy smokers and in those who will later develop clinically significant COLD. The clinical picture of cigarette-induced chronic lung injury includes three separate, but often interconnected, disease processes. They are (1) chronic mucus hypersecretion (cough and phlegm), (2) airway narrowing with expiratory airflow obstruction, and (3) abnormal dilation of the distal airspaces with destruction of alveolar walls (emphysema). Patients with severe COLD commonly have some degree of all three processes, but individual patients vary significantly in the relative contribution of the processes to their overall disease state.

Some alteration in lung structure or function is demonstrable in the majority of long-term smokers, but only a minority of smokers will develop clinically limiting COLD. In fact, only 10 to 15 percent of smokers will develop moderate or severe airflow obstruction (Bates 1973; Fletcher et al. 1976).

This chapter details the relationship between cigarette smoking and morbidity from COLD. The relationship of cigarette smoking to changes in the small airways is described first, followed by discussion of the role of smoking to chronic mucus hypersecretion, chronic airflow obstruction, and emphysema.

The tests of small airways function were developed in the late 1960s and early 1970s, and grew out of a series of studies calling attention to the functional importance of disease in the small airways. Macklem and Mead (1967) predicted that there could be considerable peripheral airway obstruction that might influence the distribution of ventilation but would have little effect on lung mechanisms; subsequently, Anthonisen et al. (1968) and Ingram and Schilder (1967) demonstrated the existence of early functional changes in smokers. These investigators showed that in a group of patients with clinically mild chronic bronchitis and normal lung function measured by spirometric tests, all had abnormalities of regional gas exchange, as determined by Xenon[133]. They attributed this finding to peripheral airway disease and suggested that the functionally important lesion in chronic bronchitis may be in the small airways. Brown and coworkers (1969), using excised lobes of dog and pig lung, demonstrated that considerable obstruction may be present in the airways smaller than 2 mm with little or no effect on overall pulmonary resistance. Hogg and coworkers (1968), using a retrograde catheter technique, measured central and peripheral airway resistance in excised normal and emphysematous human lungs and found that the peripheral airway resistance (accounting for only 25 percent of total airway resistance in the normal lungs (Macklem and Mead 1967)) was greatly increased in the lungs with emphysema. In an early structure–function correlation study, these investigators correlated the physiologic findings with histologic and bronchographic evidence of mucus plugging and narrowing and obliteration of small airways. Woolcock and coworkers (1969) reported that a group of bronchitic subjects with normal responses to routine lung function tests (lung volumes, flow rates, and diffusing capacity) demonstrated a decrease in the dynamic-to-static compliance ratio with increasing breathing frequency. These studies provided clear evidence that there can be measurable obstruction in airways 2 mm in diameter or smaller with little or perhaps no detectable influence on total airway resistance, and, therefore, on lung function measured by conventional tests such as lung volumes, spirometry, and diffusing capacity.

With the concept of small airways disease firmly established, a number of new tests considered capable of detecting the abnormality were introduced, along with reinterpretation of existing tests. The new measures included frequency dependence of compliance, the single breath N_2 test for the measurement of closing volumes (closing volume as a percent of vital capacity [CV/VC%] and closing capacity as a percent of total lung capacity [CC/TLC%]), the slope of the alveolar plateau, maximal expiratory flow volume (MEFV) curves using gases of different densities, and moment analysis of the forced

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expiration. The measurements obtained from the MEFV curve, breathing gases of different densities, are (a) the difference in maximal flow at 50 and 75 percent of the forced vital capacity breathing air and breathing a helium-oxygen (HeO_2) mixture ($\Delta \dot{V}_{max50\%}$ and $\Delta \dot{V}_{75\%}$), and (b) a measurement of the lung volume at which the air and HeO_2 curves cross, the volume of isoflow ($Viso\dot{V}$). Tests already in common use included the volume–time curve (the spirogram) and the MEFV curve breathing air. The measurements obtained from standard tests that were thought to be sensitive to mild airflow obstruction are (a) from the spirogram, the forced expiratory flow between 75 and 85 percent of the forced vital capacity ($FEF_{75-85\%}$); and (b) from the MEFV curve: maximal flow at 50 and 75 percent of the forced vital capacity, $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$.

The important question of structure–function correlation in tests of small airways function has received much attention over the past 5 years, and has been addressed via a series of attempts to correlate physiologic tests with the actual structural changes observed in lobes or lungs obtained at thoracotomy or post mortem.

Fulmer and coworkers (1977) correlated measurements of dynamic compliance with measurements of small airway diameter obtained from lung biopsies in patients with idiopathic pulmonary fibrosis. These investigators demonstrated a highly significant correlation between dynamic compliance and an overall estimate of small airways diameter.

Cosio and coworkers (1978) and Berend et al. (1979) did pulmonary function tests before lung resection and correlated the function tests with morphologic abnormalities that divided the subjects into four groups based on increasing degree of pathologic change. They found that an index of overall histologic small airways disease could be related to CC/TLC, $Viso\dot{V}$, and the slope of the alveolar plateau of the single breath N_2 test (Figure 1); inflammation, fibrosis, and squamous metaplasia were the most important lesions. The important conclusions that can be drawn from this study are that abnormalities of both spirometry and the special tests of small airways function are associated with structural changes in the peripheral airways, and that inflammation is the most important cause of obstruction to flow in small airways dysfunction.

Berend and coworkers (1979) noted a significant relationship between narrowing of the peripheral airways and CV/VC and $FEF_{25-75\%}$. In contrast to the study of Cosio et al. (1978), the slope of the alveolar plateau did not correlate with peripheral airway narrowing, and the volume of isoflow was essentially useless because of its high variability. They found that the FEV_1 was also related to peripheral airway narrowing.

Berend (1982) has recently provided new information by reanalysis and expansion of his earlier study. In measurements of small and

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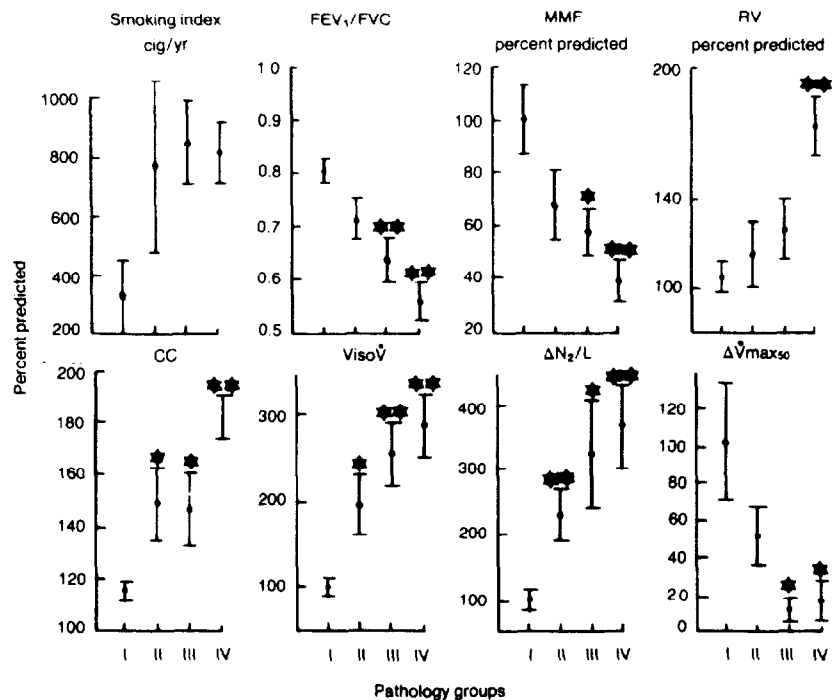
FIGURE 1.—Comparison of increasing small airways disease (Groups I to IV) to smoking index and various pulmonary function tests, by mean ± S.E.

* P < 0.05.
** P < 0.01.
SOURCE: Cosio et al. (1978).

TABLE 1.—Correlation coefficients (r) between morphologic variables and tests of pulmonary function

	FEV₁	MMFR	$\dot{V}_{50}$	R_L	Slope phase III	CV/VC	T_L CO
Bronchiolar diameter	0.28	0.37	0.48[1]	−0.36	−0.06	−0.03	0.20
Total path score	−0.39	−0.42[1]	−0.48[1]	0.03	0.22	0.30	—
Inflammation score	−0.55[2]	−0.46[1]	−0.41	0.17	0.61[2]	0.50[1]	—
Reid index	−0.50[1]	−0.41	−0.34	0.31	0.06	0.07	−0.37
Emphysema	−0.33	−0.45[1]	−0.43	0.28	0.45	0.19	−0.72[3]

[1] P < 0.05.
[2] P < 0.01.
[3] P < 0.001.

large airway lesions, he found that inflammation correlates best with the slope of the alveolar plateau, FEV_1, CV/VC, and the $FEF_{25-75\%}$ (Table 1).

Petty and coworkers (1981) studied a younger group of subjects (average age, 32) who came to autopsy. They found that inflamma-

tion and increased muscle in the small airways correlate with CC/TLC and that the slope of the alveolar plateau correlates with inflammation, increased muscle in the small airways, and increased intraluminal cells and mucus.

Berend and Thurlbeck (1982) obtained volume–pressure and MEFV curves with air and HeO_2 in 25 excised human lungs obtained at autopsy from nonhospitalized patients (age 57, ±13 years) who died suddenly from nonrespiratory causes. The emphysema grade was measured, and the total pathological score was determined from four variables: inflammation, smooth muscle hyperplasia, fibrosis, and pigmentation. Correlations were then made between the measurements obtained from the MEFV curves with air and HeO_2 and the morphology. A significant correlation was obtained between maximal flow ($\dot{V}_{max}$) and the inflammation score, fibrosis score, and emphysema grade. Small airways dimensions correlated poorly with $\dot{V}_{max\ 75\%}$ and $\dot{V}_{max\ 50\%}$, and $Viso\dot{V}$ showed no significant correlation with any small airways measurement or score.

Cosio and coworkers (1980) have also studied lungs obtained at autopsy, but did not attempt to provide structure–function correlation. They examined the lungs of smokers and nonsmokers and showed that structural changes in the small airways are more severe in smokers than in nonsmokers, with the main lesions being inflammation, goblet cell metaplasia, and hypertrophied muscle. In smokers, all the airways less than 2 mm were about equally involved. This study used slightly older subjects than an earlier study by the same investigators. In the earlier study, goblet cell metaplasia, increased smooth muscle, and airway narrowing were not observed, suggesting that perhaps these lesions are a later stage in the evolution of the response to injury in the small airways.

In another study of lungs obtained at autopsy, Salmon and coworkers (1982) correlated morphologic measurements of the central and peripheral airways and the alveolar surface-to-volume ratio with the slope of the alveolar plateau measured in the lung post mortem. They found a significant inverse correlation between the slope of the alveolar plateau and the peripheral airway diameter, but no significant relationship between the slope of the alveolar plateau and the alveolar-to-surface volume ratio, once age had been controlled. They concluded from these findings that the slope of the alveolar plateau does indeed assess the properties of the peripheral airways.

Mink and Wood (1980) performed physiologic studies on the lungs of six men (average age, 66 years) who died of atherosclerotic heart disease. Morphometrics were performed on one lung of each of two of the subjects. The physiologic studies involved ventilating a lung through a main-stem bronchus in a volume displacement plethysmograph with two catheters placed to record pressure: one in the lower